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CMR Imaging Assessing Viability in Patients With Chronic Ventricular Dysfunction Due to Coronary Artery Disease

A Meta-Analysis of Prospective Trials

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OBJECTIVES The purpose of this study was to compare the diagnostic accuracy of cardiac magnetic resonance (CMR) assessing myocardial viability in patients with chronic left ventricular (LV) dysfunction due to coronary artery disease using 3 techniques: 1) end-diastolic wall thickness (EDWT); 2) low-dose dobutamine (LDD); and 3) contrast delayed enhancement (DE).

BACKGROUND CMR has been proposed to assess myocardial viability over the past decade. However, the best CMR strategy to evaluate patients being contemplated for revascularization has not yet been determined. Some centers advocate DE CMR due to its high sensitivity to identify scar, whereas others favor the use of LDD CMR for its ability to identify contractile reserve.

METHODS A systematic review of MEDLINE, Cochrane, and Embase for all the prospective trials assessing myocardial viability in subjects with chronic LV dysfunction using CMR was performed using a standard approach for meta-analysis for diagnostic tests and a bivariate analysis of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

RESULTS A total of 24 studies of CMR evaluating myocardial viability with 698 patients fulfilled the inclusion criteria. Eleven studies used DE, 9 studies used LDD, and 4 studies used EDWT. Our meta-analysis indicates that among CMR methods, DE CMR provides the highest sensitivity as well as the highest NPV (95% and 90%, respectively) for predicting improved segmental LV contractile function after revascularization, followed by EDWT CMR, whereas LDD CMR demonstrated the lowest sensitivity/NPV among all modalities. On the other hand, LDD CMR offered the highest specificity and PPV (91% and 93%, respectively), followed by DE CMR, whereas EDWT showed the lowest of these parameters.

CONCLUSIONS DE CMR provides the highest sensitivity and NPV, whereas LDD CMR provides the best specificity and PPV. In light of these findings, integrating these 2 methods should provide increased accuracy in evaluating patients with chronic LV dysfunction being considered for revascularization. (J Am Coll Cardiol Img 2012;5:494–508) © 2012 by the American College of Cardiology Foundation

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Shortly after the phrase *hibernating myocardium* was introduced in 1986 and the possibility for detection of salvageable myocardium in coronary artery disease (CAD) was identified (1), several different methods of assessing myocardial viability have been implemented and tested. Viability tests have become a crucial tool in evaluating whether patients with congestive heart failure related to CAD might benefit from revascularization therapy. Revascularization is accomplished

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in the form of either coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI) (2), both of which have been proven to be superior to medical therapy in optimizing cardiac contractility (3).

The most studied noninvasive techniques for evaluating myocardial viability are dobutamine stress echocardiography (DSE), positron emission tomography with fluorine-18 deoxyglucose (PET-FDG), single-photon emission computed tomography (SPECT) with thallium-201 stress–redistribution–reinjection, thallium-201 late redistribution, and technetium-99m sestamibi (4). These modalities rely on the demonstration of wall motion abnormalities, preserved myocardial metabolism, cell membrane integrity, and intact mitochondrial function in assessing the patient's myocardial viability, respectively (5–7). Bax et al. (8) published 2 meta-analyses evaluating the accuracy of the aforementioned techniques; the first study in 1997 concluded that DSE had overall the highest predictive accuracy in assessing myocardial viability. His second study in 2001 concluded that nuclear imaging rendered higher sensitivities and negative predictive values (NPV), whereas dobutamine echocardiography provided higher specificities and positive predictive values (PPV) (9).

Over the past decade, newer techniques such as magnetic resonance imaging (MRI), electroanatomic mapping, and myocardial contrast echocardiography have been proposed to assess myocardial viability (10–12). Cardiac magnetic resonance (CMR) has gained popularity due to technological innovations such as electrocardiographic gating and respiratory motion suppression methods, which facilitate high-quality cross-sectional images of the heart with superior spatial resolution (13). Unlike other imaging modalities, CMR has the advantage of detecting the percentage of transmural involvement in the ventricular wall, differentiating transmural from subendocardial infarcts (10).

Previous investigations have fundamentally evaluated 3 CMR methods: 1) resting assessment of left ventricular (LV) end-diastolic wall thickness (EDWT); 2) low-dose (LDD) dobutamine stress assessment of contractile reserve; and 3) delayed contrast enhancement (DE) to assess for scar tissue (14–16). To date, there have been 3 reviews regarding CMR and myocardial viability in which pooled data from previous original investigators were displayed (17–19). More recently, Schinkel et al. (20) updated the work done by Bax et al. (8,9) and also included CMR as a new technique in their analyses. Nevertheless, these included only a limited number of studies in each CMR modality, and significant differences among studies were not accounted for. In the following meta-analysis, we scrutinize the accuracy of different techniques using CMR in the evaluation of myocardial viability in the extensive literature on this modality.

ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass graft
CAD = coronary artery disease
CI = confidence interval
CMR = cardiac magnetic resonance
DE = contrast delayed enhancement
DSE = dobutamine stress echocardiography
EDWT = end-diastolic wall thickness
LDD = low-dose dobutamine
LV = left ventricular
MRI = magnetic resonance imaging
NPV = negative predictive value
PCI = percutaneous coronary intervention
PET-FGD = positron emission tomography with fluorine-18 deoxyglucose
PPV = positive predictive value
QUADAS = quality assessment of diagnostic accuracy studies instrument
ROC = receiver-operating characteristic
SPECT = single-photon emission computed tomography

METHODS

Search strategy. The objective of the current analysis was to evaluate the available prospective trials in which CMR, using at least 1 of the 3 aforementioned methods, assessed LV regional and global function after revascularization.

We searched PubMed, Embase, and the Cochrane Central Register of Clinical Trials (Cochrane Library, Issue 1, 2011) using the terms (*MRI* OR *magnetic resonance imaging* OR *magnetic resonance* OR *magnetic resonance spectroscopy* OR *cardiac magnetic resonance* OR *cardiovascular magnetic resonance* OR *contrast-enhanced MRI*) AND (*viability* OR *myocardial viability* OR *cardiac viability* OR *viability assessment* OR *viability test* OR *viable myocardium* OR *ventricular dysfunction* OR *myocardial dysfunction* OR *cardiac dysfunction* OR *ejection fraction* OR *dysfunctional myocardium* OR *functional recovery* OR *hibernating myocardium*). We limited our search to humans and adults (older than 19 years of age) in peer-reviewed journals from 1966 to June 2011. No language restriction was applied. The reference lists of bibliographies of identified articles were also reviewed. Trials in the abstract form without a manuscript published were excluded from this analysis.

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Selection criteria. To be included in the analysis, a trial had to fulfill the following criteria: 1) prospective study involving patients with CAD in whom a) CMR was performed before revascularization (i.e., PCI or CABG) in order to assess viability, and b) any current standard evaluation technique for left ventricular regional and/or global function was performed to assess improvement after revascularization; 2) assessment of viability was performed in patients only with chronic stable LV dysfunction at least 2 weeks after myocardial infarction to avoid stunning myocardium; 3) study allowed for sensitivity, specificity, NPV, and PPV calculations; and 4) there was use of standardized cutoffs for each technique, or the study provided enough data to calculate diagnostic and predictive accuracies using these cutoffs.

Data extraction. Two investigators (J.R. and W.G.) extracted the data independently and in duplicate. Data was extracted using standardized protocol and reporting forms. Disagreements were resolved by arbitration (J.R. or M.J.G.), and consensus was reached after discussion. We extracted characteristics of each trial, interval between revascularization and follow-up CMR, methods, baseline demographics, and number of viable and nonviable segments predicted at baseline and after the revascularization for our analysis. In instances where these values were not readily available, the main investigator of that particular trial was approached to supply the relevant information.

Quality assessment. To assess the quality and reporting of studies, we evaluated 14 items that were considered relevant to the review topic, based on the quality assessment of diagnostic accuracy studies instrument (QUADAS) (21). Two reviewers (J.R. and W.G.) independently assessed the quality items, and discrepancies were resolved by consensus. These items covered patient spectrum, reference standard, disease progression bias, verification bias, review bias, clinical review bias, incorporation bias, test execution, study withdrawals, and indeterminate results.

Statistical analysis. Sensitivities (number of viable segments estimated by the test divided by the total number of segments with improved function after revascularization), specificities (number of nonviable segments estimated by the test divided by the total number of segments without improved function after revascularization), PPV (segments with recovery after revascularization divided by test-viable segments), and NPV (segments without recovery after revascularization divided by test-nonviable segments) were calculated for every study.

Several methods for meta-analysis of diagnostic tests have been developed lately. Some methods are designed to be used with individual patient data of the studies. Some methods are applicable when only sensitivity and specificity for each study is available, such as the situation in this paper, which is most commonly seen in practice. A commonly used and standard method for such situation is the summary receiver-operating characteristic (ROC) method (22,23). This approach coverts each pair of sensitivity and specificity values into a single measure of accuracy, the diagnostic odds ratio. However, summary ROC does not distinguish between the ability of detecting the sick (sensitivity) and identifying the well (specificity). Discriminating between these abilities is important to determine the optimal use of a test in clinical practice. Therefore, in this meta-analysis, we estimated summary sensitivity and specificity using a more recently developed bivariate random effects model instead (24).

The bivariate approach assumed logit transforms of sensitivity and specificity from individual studies are from a bivariate normal distribution. The bivariate approach is considered to be a better approach as compared with the standard summary ROC approach because first, it assesses heterogeneity across studies in sensitivity and specificity, and provides a summary estimate of sensitivity and specificity; second, it models sensitivity and specificity jointly so that a 95% confidence ellipse around the summary estimate can be calculated; third, it allows one to directly compare sensitivity and specificity between methods; further, several choices are available to obtain a summary ROC curve (24,25). In this paper, the summary ROC curve was obtained by transforming the regression line of logit sensitivity on logit specificity into ROC space (25). A similar bivariate approached was used to model PPV and NPV (26). Publication bias was assessed for each technique using Egger's, Macaskill's, and Deeks's methods. Deeks et al. (27) recently pointed out that Egger's and Macaskill's methods may be misleading because their type I error rates are typically inflated and can have low power when diagnostic odds ratios are heterogeneous.

We assessed between-study heterogeneity visually, by plotting sensitivity and specificity in the ROC curves. We also drew summary ROC curves and confidence regions for summary sensitivity and specificity (24,28).

The analyses were conducted using SAS (SAS version 9.2, 2002 to 2008, SAS Institute, Cary, North Carolina), and the figures were generated using R (R version 2.12.2, 2011, The R Foundation for Statistical Computing, Vienna, Austria).

Sensitivity analysis. We further evaluated whether the performance of each technique depends on features of the technique and patient characteristics. A logistic regression for each technique was used to model the sensitivity on these factors. For DE CMR, the standard deviation cutoff value, the follow-up time after the procedure and the proportion of males and average age for the study population were examined. No factor has been identified that had a significant influence on its sensitivity; for LDD, the follow-up time after the procedure and the proportion of males in the study population had a significant impact on its sensitivity ($p < 0.001$ for both): the longer the follow-up time and the more men in the study, the higher the sensitivity; for EDWT, the follow-up time, the proportion of males in the study, and the mean age of the population all had a significant impact on its sensitivity; however, the longer the follow-up and the more men in the study, the lower the sensitivity. But older age is associated with higher sensitivity for EDWT, and the cutoff value (5.5 vs. 6.0) for viability is not associated with its sensitivity.

RESULTS

Study selection. We identified 12,200 articles, out of which 8,705 abstracts were retrieved and reviewed for possible inclusion (Fig. 1). Twenty-four studies (Tables 1, 2, and 3) enrolling 698 patients (mean age 62 years; 83% men) and a total of 6,404 LV segments fulfilled the inclusion criteria and were included in the analysis. Fourteen studies were excluded from the final analysis because they did not meet the inclusion criteria: 5 used a different CMR technique (pixel-tracking–derived myocardial deformation imaging [29], regional systolic myocardial strain [30,31], diffusion-tensor CMR [32], and non–contrast-enhanced myocardial rim [33]); 3 DE CMR studies used a different cutoff (34–36); 3 studies provided no data to calculate diagnostic accuracies (37–39); 2 LDD CMR studies had no data available to calculate sensitivity/specificity (40,41); 1 study used high-dose dobutamine 15 μg/kg/min (42); and an EDWT study did not provide data to calculate diagnostic accuracies (43).

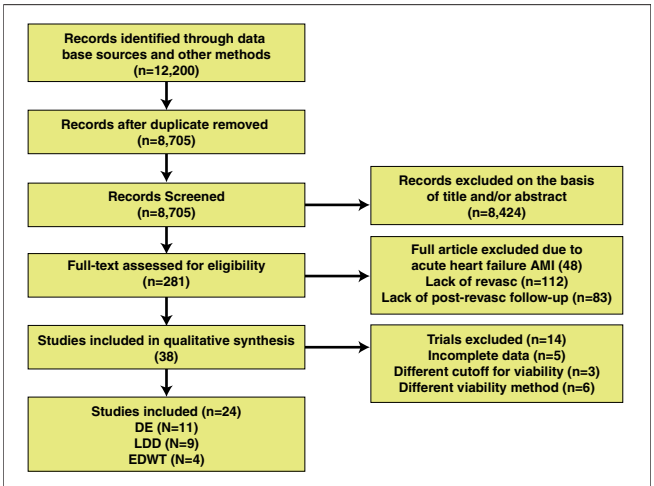

Figure 1. Selection of Studies

Fourteen studies were excluded from the final analysis: 5 used a different CMR technique (pixel-tracking–derived myocardial deformation imaging [29], regional systolic myocardial strain [30,31], diffusion-tensor CMR [32], non–contrast-enhanced myocardial rim [33]), 3 DE CMR studies used a different cutoff (34–36), 3 studies provided no data to calculate diagnostic accuracies (37–39), 2 LDD CMR studies had no data available to calculate sensitivity/specificity (40,41), 1 study used high-dose dobutamine 15 μg/kg/min (42), and an EDWT study did not provide data to calculate diagnostic accuracies (43). AMI = acute myocardial infarction; CMR = cardiac magnetic resonance; DE = contrast delayed enhancement; EDWT = end-diastolic wall thickness; LDD = low-dose dobutamine.

Baseline characteristics. Of the 24 studies, 11 studies (10,44–53) enrolling 331 patients (mean age 64 years; 83% men) and analyzing 4,397 LV segments evaluated myocardial viability using DE CMR, 10 studies used cine-CMR for follow up, and only 1 used echocardiography. Nine studies (36,45,51,54–59) with 247 patients (mean age 62 years; 79% men) and 1,120 LV segments evaluated myocardial viability using LDD CMR with all of them using cine-MRI for follow up, and 4 studies (45,55,59,60) with 120 patients (mean age 57 years; 92% men) and 887 LV segments evaluated myocardial viability using EDWT CMR (Tables 1, 2, and 3).

Quality assessment. Reporting was especially poor on item 11 ("Were the reference standard results interpreted without knowledge of the results of the index test?"); this refers to blinding and might have led to inflated measures of diagnostic accuracy, which is known as a review bias. Twelve percent of the articles did not explain withdrawals from the studies, indicating that test performance may introduce a bias. Otherwise, all the studies showed high-quality scores in the remaining 12 items of QUADAS (Figs. 2 and 3).

Table 1. Baseline Characteristics of Studies Included in the Meta-Analysis Using CMR With DE

First Author (Ref #), Year	Study Design	n	Male (%)	Age (yrs)	LVEF (%)	Revascularization	Follow-Up MRI (Weeks)	Technique to Assess LVEF	Time After Gadolinium Administration (min)	Hyperenhancement (SD Above Normal Intensity)	Cutoff for Viability (%)
Becker et al. (44), 2008	Prospective	21	62	59	41	CABG/PCI	36	CMR	15	>3	<50
Bondarenko et al. (53), 2007	Prospective	36	84	62	39	CABG	12	CMR	13	>5	<50
Gutberlet et al. (45), 2005	Prospective	20	95	64	29	CABG	24	CMR	15	>2	<50
Kim et al. (10), 2000	Prospective	43	88	63	43	CABG/PCI	11	CMR	NR	>6	<50
Kuhl et al. (46), 2006	Prospective	29	72	66	32	CABG/PCI	24	CMR	15	>3	<50
Pegg et al. (47), 2010	Prospective	33	94	66	38	CABG	24	CMR	6	>2	<50
Sandstede et al. (48), 2000	Prospective	12	83	61	NR	CABG/PCI	12	CMR	15	NR	<50
Schvartzman et al. (49), 2003	Prospective	29	79	62	28	CABG	6	ECHO	25	NR	<50
Selvanayagam et al. (50), 2004	Prospective	52	NR	NR	62	CABG	24	CMR	10	>2	<50
Wellnhofer et al. (51), 2004	Prospective	29	93	68	NR	CABG/PCI	12	CMR	13	NR	<50
Wu et al. (52), 2007	Prospective	27	78	66	38	CABG	24	CMR	15	NR	<50

CABG = coronary artery bypass graft; CMR = cardiac magnetic resonance; DE = contrast delayed enhancement; DSE = dobutamine stress echocardiography; ECHO = echocardiography; LVEF = left ventricular ejection fraction; NR = not reported.

Publication bias. Using Egger's or Macaskill's methods, there is no indication of publication bias for any of the 3 techniques. Likewise, Using Deeks's test, there is no indication of publication bias for DE and EDWT CMRs ($p = 0.43$ and 0.47, respectively). However, a borderline significance indicates that there might be some possibility of publication bias in LDD CMR ($p = 0.05$). This indicates that some studies reporting negative results for this technique might not have been submitted for publication, and if they were, they were never published.

Delayed enhancement CMR. A total of 11 studies evaluated myocardial viability using DE. The follow-up CMR was performed between 6 and 36 weeks (mean 19 weeks) after revascularization. This difference in follow-up did not reach statistical significance. Also, some studies used a different standard deviation to define hyperenhancement, ranging from 2 to 6 SD (mean of 3.28 SD), which did not show any significance. Gadolinium was administered as a contrast in all studies, and images were obtained 6 to 25 min after administration.

Table 2. Baseline Characteristics of Studies Included in the Meta-Analysis Using CMR With LDD

First Author (Ref #), Year	Study Design	n	Male (%)	Age (yrs)	LVEF (%)	Revascularization	Follow-Up CMR (Weeks)	Technique to Assess LVEF	Dobutamine Dose (μg/kg/min)	Cutoff for Viability (mm)
Baer et al. (55), 1998	Prospective	43	93	58	42	CABG/PCI	20	CMR	10	>2
Baer et al. (54), 2000	Prospective	52	48	58	41	CABG/PCI	NR	CMR	5–10	>2
Gutberlet et al. (45), 2005	Prospective	20	95	64	29	CABG	24	CMR	5–10	>2
Lauerma et al. (56), 2000	Prospective	10	80	69	44	PCI	24	CMR	5	>2
Sandestede et al. (57), 1999	Prospective	25	88	58	NR	CABG/PCI	12	CMR	10	>2
Sayad et al. (58), 1998	Prospective	10	70	NR	NR	CABG/PCI	6	CMR	5–10	>2
Schmidt et al. (59), 2004	Prospective	40	92	57	42	CABG/PCI	20	CMR	10	>2
Van Hoe et al. (36), 2004	Prospective	18	56	62	52	CABG/PCI	36	CMR	10	>2
Wellnhofer et al. (51), 2004	Prospective	29	93	68	NR	CABG/PCI	12	CMR	5–10	>2

LDD = low-dose dobutamine; other abbreviations as in Table 1.

Table 3. Baseline Characteristics of Studies Included in the Meta-Analysis Using CMR With EDWT

First Author (Ref #), Year	Study Design	n	Male (%)	Age (yrs)	LVEF (%)	Revascularization	Follow-Up CMR (Weeks)	Technique to Assess LVEF	Cutoff for Viability (mm)
Baer et al. (55), 1998	Prospective	43	93	58	42	CABG/PCI	20	CMR	>5.5
Gutberlet et al. (45), 2005	Prospective	20	95	64	29	CABG	24	CMR	>6
Klow et al. (60), 1997	Prospective	17	88	63	40	CABG	88	CMR	>6
Schmidt et al. (59), 2004	Prospective	40	92	57	42	CABG/PCI	20	CMR	>5.5

EDWT = end-diastolic wall thickness; other abbreviations as in Table 1.

All the studies included used 50% of LV wall hyperenhancement as a cutoff to determine whether or not a LV segment was viable (i.e., <50% hyperenhancement was deemed viable and >50% hyperenhancement was deemed nonviable). The weighted mean sensitivity and specificity were 95% (95% confidence interval [CI]: 93% to 97%) and 51% (95% CI: 40% to 62%), whereas the PPV was 69% (95% CI: 56% to 80%) and NPV was 90% (95% CI: 85% to 93%) (Table 4). This technique had a weighted overall accuracy of 70% (95% CI: 69% to 71%).

DE CMR using <0%, <25%, and <75% as cutoffs. Of the 11 studies evaluating hibernating myocardium using DE CMR, only 6 studies reported their results by quartiles. A total of 214 patients and 3,365 LV segments were analyzed.

CUTOFF <0%. The weighted sensitivity and specificity for this cutoff were 0.53 (95% CI: 0.50 to 0.55) and 0.87 (95% CI: 0.85 to 0.88), whereas the PPV and NPV were 0.77 (95% CI: 0.75 to 0.80) and 0.68 (95% CI: 0.66 to 0.70), respectively.

CUTOFF <25%. The weighted sensitivity and specificity were 0.78 (95% CI: 0.76 to 0.80) and 0.71 (95% CI: 0.69 to 0.73), whereas the PPV and NPV were 0.70 (95% CI: 0.67 to 0.72) and 0.79 (95% CI: 0.77 to 0.81), respectively.

CUTOFF <75%. The weighted sensitivity and specificity for this cutoff were 0.99 (95% CI: 0.99 to 1.00) and 0.21 (95% CI: 0.19 to 0.22), whereas the PPV and NPV were 0.52 (95% CI: 0.50 to 0.54) and 0.97 (95% CI: 0.96 to 0.99), respectively.

Dobutamine stress CMR. A total of 9 studies were evaluated using this method to evaluate for myocardial viability. Each study used a 2-mm change in LV wall motion during LDD infusion (5 to 10 μg/kg/min) as a cutoff to classify a segment as viable or not. Each study performed the second CMR also between 6 and 36 weeks (mean 19 weeks) after revascularization. There was no statistical difference in terms of revascularization procedure (CABG vs. PCI). In these studies, the mean weighted sensitivity and specificity were 81% (95% CI: 73 to 86) and 91% (95% CI: 84% to 95%), whereas the PPV and NPV were 93% (95% CI: 87% to 97%) and 75% (95% CI: 65% to 83%), respectively (Table 5). The weighted overall accuracy for this technique was 84% (95% CI: 82% to 86%).

EDWT CMR. Only 4 studies fulfilled the inclusion criteria for this method. The cutoff used was EDWT of 5.5 to 6.0 mm for each study. The follow-up CMR was performed between 20 to 88 weeks (mean 38 weeks). The mean weighted sensitivity and specificity were 96% (95% CI: 91% to 98%) and 38% (95% CI: 23% to 57%), whereas the PPV and NPV were 71% (95% CI: 49% to 86%) and 85% (95% CI: 70% to 93%), respectively (Table 6). EDWT CMR had a weighted overall accuracy of 68% (95% CI: 66% to 70%).

The bivariate model showing summary diagnostic accuracies and comparing every method versus each other are shown in Table 7. Forest plots and ROC curves are displayed in Figures 4A to 4C and 5A to 5C, respectively.

DISCUSSION

In modern medicine, viability tests are routinely performed on subjects in whom revascularization is being considered. Allman et al. (61) demonstrated a strong association between viable myocardium on noninvasive testing and increased survival after revascularization with a reduction in annual mortality of 79.6% compared with medical therapy (3.2% vs. 16%). Hence, the 2009 guidelines for the diagnosis and management of heart failure in adults by the American College of Cardiology and the American Heart Association recommend noninvasive imaging in patients with heart failure who have known CAD and no angina (Class IIa, Level of Evidence: B), based on the fact that CABG or PCI is recommended in patients with chest pain regard-

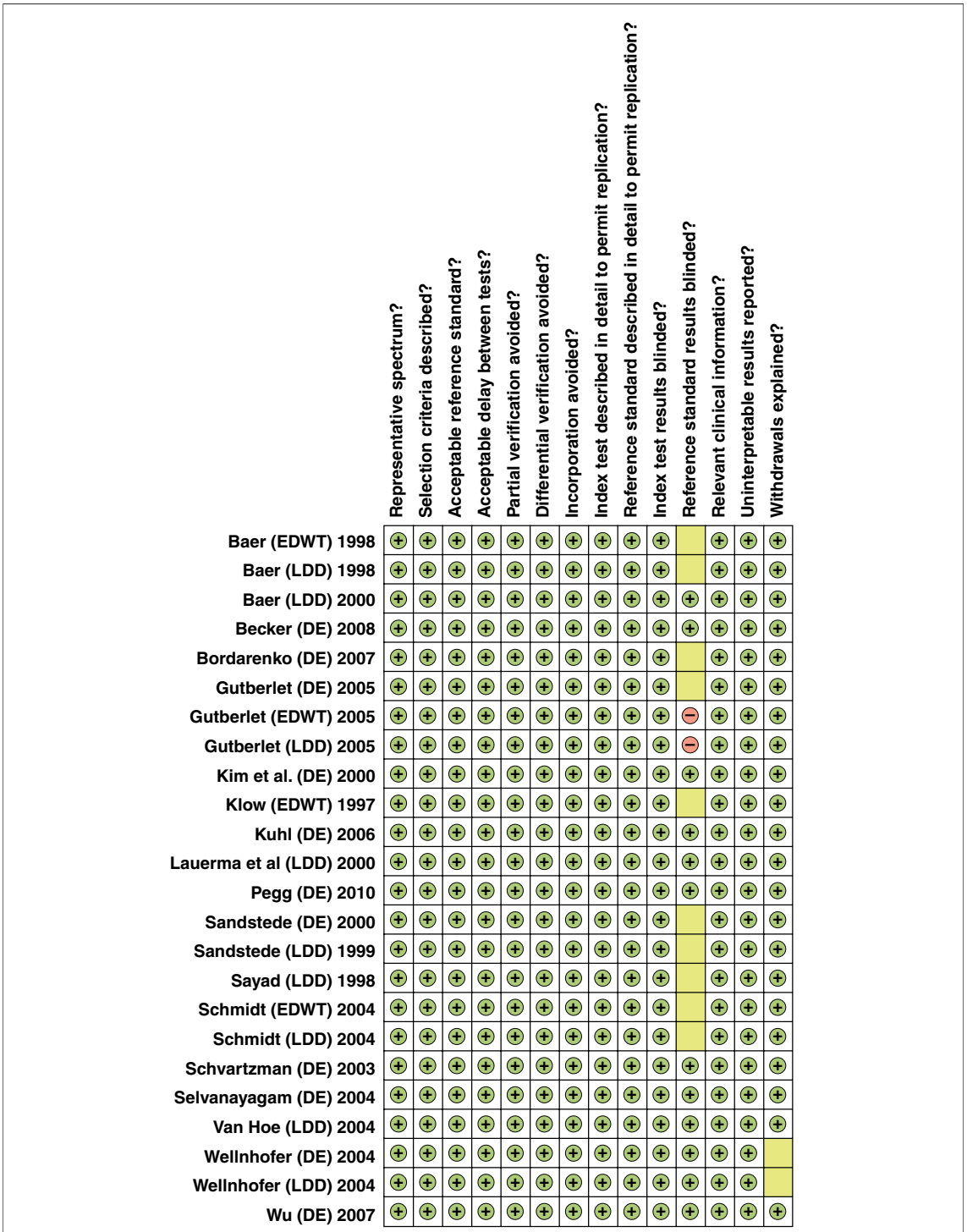

Figure 2. Methodological Quality Summary

Good (+), indeterminate or poor (−) quality.

QUADAS = quality assessment of diagnostic accuracy studies; other abbreviations as in Figure 1.

less of the degree of ischemia or viability (62). Nonetheless, no assessment modality is specified as preferable because most of them have similar diagnostic accuracies, and each has shortcomings, with none of them near to be perfect. Some series have suggested that CMR may be a more accurate

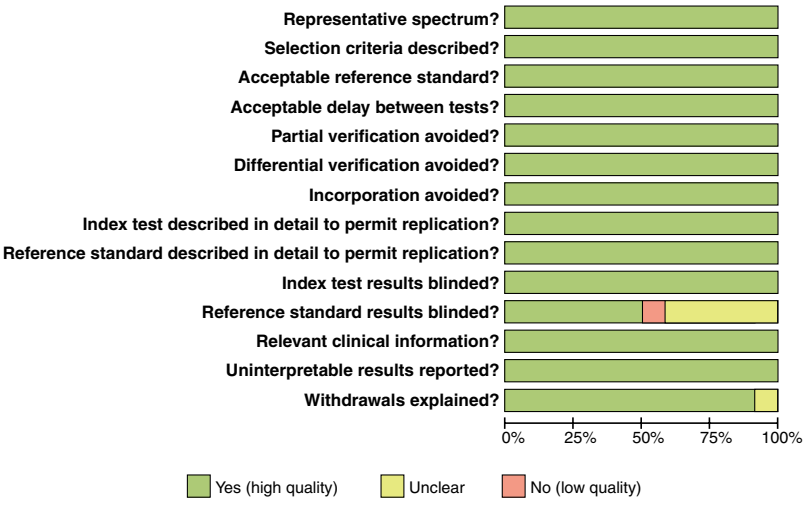

Figure 3. Methodological Quality Graph

Reporting was especially poor on item 11 ("Were the reference standard results interpreted without knowledge of the results of the index test?"); this refers to blinding and might have led to inflated measures of diagnostic accuracy, which is known as a review bias. Twelve percent of the articles did not explain withdrawals from the studies indicating that test performance may introduce a bias. Otherwise, all the studies showed high-quality scores in the remaining 12 items of QUADAS (quality assessment of diagnostic accuracy studies).

modality, but these claims have not been systematically evaluated. The current study aimed at comparing the diagnostic and predictive accuracies of 3 different assessment methods that have been studied.

Our meta-analysis indicates that among CMR methods, DE CMR provides the highest sensitivity as well as the highest NPV for predicting improved segmental LV contractile function after revascularization, followed by EDWT CMR, whereas LDD CMR demonstrated the lowest sensitivity/NPV among all modalities. On the other hand, LDD CMR offered the highest specificity and PPV, followed by DE CMR, whereas EDWT showed the lowest of these parameters. LDD CMR also provided the highest diagnostic odds ratio, suggesting that it has the best overall performance; however, the difference with the other 2 methods is not statistically significant, therefore this result needs to be interpreted cautiously.

By comparing these values with those reported for 4 different imaging modalities in 2 compelling meta-analyses published by Bax et al. (9) and Schinkel et al. (20), it is clearly seen that DE CMR

Table 4. Sensitivities/Specificities and Predictive Values of DE CMR

First Author (Ref #), Year	Sensitivity (%) Segments	Specificity (%) Segments	PPV (%) Segments	NPV (%) Segments
Becker et al. (44), 2008	95 (215/227)	42 (100/236)	61 (215/351)	89 (100/122)
Bordarenko et al. (53), 2007	93 (79/85)	38 (92/237)	35 (79/224)	94 (92/98)
Gutberlet et al. (45), 2005	99 (198/200)	94 (30/32)	99 (198/200)	98 (30/32)
Kim et al. (10), 2000	97 (411/425)	44 (168/379)	66 (411/622)	92 (168/182)
Kuhl et al. (46), 2006	98 (94/96)	70 (64/91)	78 (94/121)	97 (64/66)
Pegg et al. (47), 2010	96 (381/397)	59 (332/560)	63 (381/609)	96 (332/348)
Sandstede et al. (48), 2000	97 (39/40)	76 (25/33)	83 (39/47)	96 (25/26)
Schvartzman et al. (49), 2003	94 (95/101)	25 (27/106)	55 (95/174)	81 (27/33)
Selvanayagam et al. (50), 2004	95 (323/340)	26 (71/272)	62 (323/524)	80 (71/88)
Wellnhofer et al. (51), 2004	90 (111/124)	52 (85/164)	58 (111/190)	86 (85/98)
Wu et al. (52), 2007	92 (142/154)	45 (44/98)	73 (142/196)	78 (44/56)
Weighted mean	95	51	69	90

Segments are given as % (n/N).
NPV = negative predictive value; PPV = positive predictive value; other abbreviations as in Table 1.

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Table 5. Sensitivities/Specificities and Predictive Values of Dobutamine Stress CMR

First Author (Ref #), Year	Sensitivity (%) Segments	Specificity (%) Segments	PPV (%) Segments	NPV (%) Segments
Baer et al. (55), 1998	89 (24/27)	94 (15/16)	96 (24/25)	83 (15/18)
Baer et al. (54), 2000	86 (24/28)	92 (22/24)	92 (24/26)	85 (22/26)
Gutberlet et al. (45), 2005	88 (183/208)	89 (32/36)	97 (183/187)	56 (32/57)
Lauerma et al. (56), 2000	75 (43/57)	100 (29/0)	100 (43/43)	67 (29/43)
Sandstede et al. (57), 1999	61 (65/106)	90 (91/101)	87 (65/75)	43 (91/132)
Sayad et al. (58), 1998	89 (25/28)	93 (14/15)	96 (25/26)	82 (14/17)
Trent et al. (42), 2000	71 (81/114)	70 (163/232)	54 (81/150)	83 (163/196)
Van Hoe et al. (36), 2004	78 (56/72)	82 (37/45)	88 (56/64)	70 (37/53)
Wellnhofer et al. (51), 2004	75 (93/124)	93 (152/164)	86 (93/105)	83 (152/183)
Weighted mean	81	91	93	75

Segments are given as % (n/N).
Abbreviations as in Tables 1 and 4.

provides the highest sensitivity and NPV (95% and 90%) for predicting functional improvement after revascularization of hibernating myocardium of any other technique in clinical practice (i.e., PET-FDG [92% and 87%], rest-redistribution thallium-201-SPECT [87% and 79%], technetium-99m sestamibi-SPECT [83% and 76%], and DSE [80% and 83%]). Similarly, LDD CMR provides the highest specificity and PPV (91% and 93%) compared with any other modality, including PET-FDG (63% and 74%), rest-redistribution thallium-201 SPECT (54% and 67%), technetium-99m sestamibi SPECT (65% and 74%), and DSE (78% and 75%).

Having the highest NPV, DE CMR allows for physician confidence in evaluating the appropriateness of revascularization therapy in selected patients.

Likewise, having the highest PPV, LDD CMR would prevent patients from undergoing unnecessary high-risk revascularization procedures. It has been shown that the annual mortality rate is approximately 3.2% after revascularization in patients with viable myocardium as compared with 7.7% in those without evidence of viable myocardium. Furthermore, the perioperative mortality is almost insignificant for patients with viable myocardium and as high as 10% in those without viability (63–65).

Identification of hibernating myocardium in patients with CAD and LV dysfunction was performed by Shimoni et al. (12), comparing 3 different modalities head to head: 1) myocardial contrast echocardiography; 2) thallium-201 (Tl201) scintigraphy; and 3) dobutamine echocardiography. The sensitivities for functional recovery were 90%, 92%, and 80%, respectively. On the other hand, the reported specificity for each technique was 63%, 45%, and 54%, respectively (12). In the ischemic cascade, perfusion abnormalities occur earlier than contractile abnormalities. This explains why several studies have shown higher sensitivity for nuclear perfusion imaging compared with contractile reserve (12,66). Scar formation, which is measured by DE MRI, is the last manifestation in the ischemic cascade; that is why presence of DE should have the highest sensitivity to predict absence of recovery. The superiority of CMR to echocardiography and nuclear techniques might be attributed to 2 main factors: 1) CMR has higher spatial resolution compared with SPECT or PET, by which it can provide a more precise delineation of scar tissue; and 2) contrast-enhanced echocardiography may potentially

Table 6. Sensitivities/Specificities and Predictive Values of EDWT CMR

First Author (Ref #), Year	Sensitivity (%) Segments	Specificity (%) Segments	PPV (%) Segments	NPV (%) Segments
Baer et al. (55), 1998	94 (176/188)	52 (113/219)	62 (176/282)	90 (113/125)
Gutberlet et al. (45), 2005	96 (216/225)	35 (11/31)	92 (216/236)	55 (11/20)
Klow et al. (60), 1997	98 (63/64)	19 (23/120)	40 (63/160)	96 (23/24)
Schmidt et al. (59), 2004	100 (25/25)	53 (8/15)	78 (25/32)	100 (8/8)
Weighted mean	96	38	71	85

Segments are given as % (n/N).
Abbreviations as in Tables 1, 3, and 4.

Table 7. Summary Estimates for Sensitivity, Specificity, and DOR From the Bivariate Model

CMR	Mean Sensitivity (95% CI)	Mean Specificity (95% CI)	Mean DOR (95% CI)	PPV (95% CI)	NPV (95% CI)
DE CMR	0.95 (0.93–0.97)	0.51 (0.40–0.62)	21.12 (10.98–40.55)	0.69 (0.56–0.80)	0.90 (0.85–0.93)
LDD CMR	0.81 (0.73–0.86)	0.91 (0.84–0.95)	41.57 (18.25–94.68)	0.93 (0.87–0.97)	0.75 (0.65–0.83)
EDWT CMR	0.96 (0.91–0.98)	0.38 (0.23–0.57)	13.33 (4.16–42.74)	0.71 (0.49–0.86)	0.85 (0.70–0.93)
p Value DE vs. LDD	<0.001	<0.001	0.21	<0.001	0.001
p Value DE vs. EDWT	0.89	0.25	0.34	0.87	0.37
p Value LDD vs. EDWT	<0.001	<0.001	0.08	0.01	0.21

CI = confidence interval; DOR = diagnostic odds ratio; other abbreviations as in Tables 1, 2, 3, and 4.

identify nonperfused scarred myocardial segments, but this technique is greatly limited by attenuation and bubble destruction artifacts (67–69).

On the basis of our analysis, performing a LDD CMR may be useful in high operative risk patients who have a positive DE CMR in order to obtain a

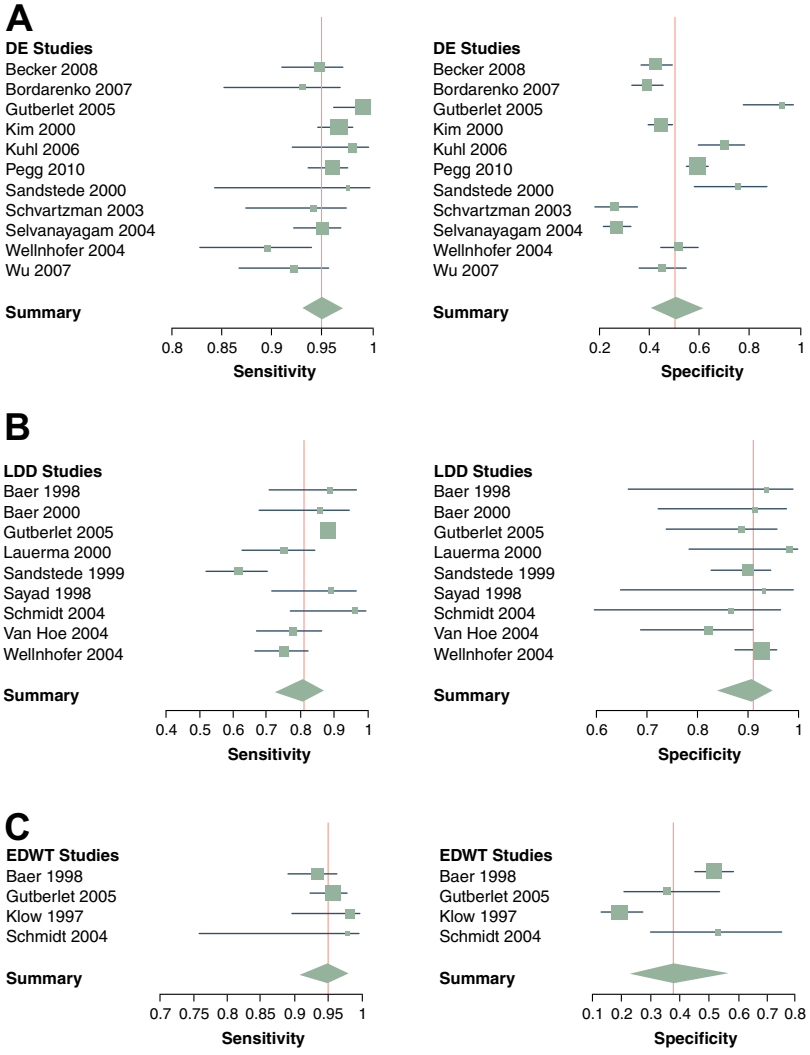
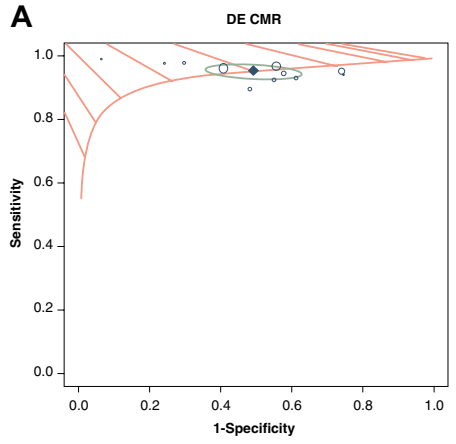
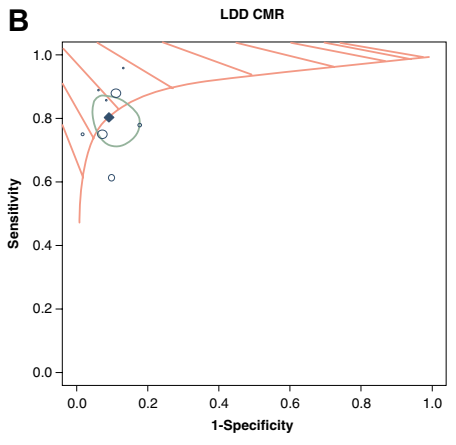


Figure 4. Forest Plots of Sensitivity and Specificity

(A) DE CMR, **(B)** LDD CMR, and **(C)** EDWT CMR: the size of the **square plotting symbol** is proportional to the same size for each study. **Horizontal lines** are the 95% confidence intervals, and the summary sensitivity and specificity are calculated based on the bivariate approach. Abbreviations as in Figure 1.





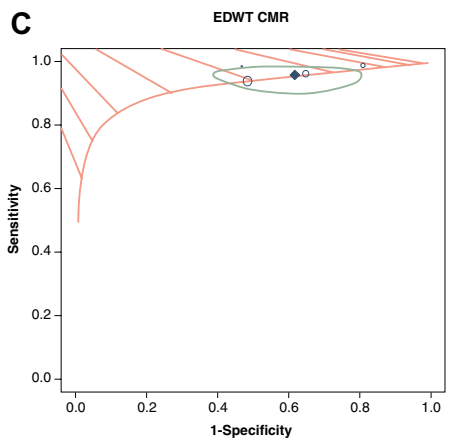


Figure 5. ROC Curves

Bivariate summary estimate of sensitivity and specificity for **(A)** DE CMR, **(B)** LDD CMR, and **(C)** EDWT CMR and the corresponding 95% confidence **ellipse** around its mean value. The **solid square** in the center represents the mean specificity and specificity. Each **circle** represents an individual study, whereas the size of each **circle** is proportional to the sample size for each study. The **solid curve** is the summary receiver-operating characteristic (ROC) curve. Abbreviations as in Figure 1.

higher specificity and thus higher PPV. Conversely, DE CMR could similarly be added to LDD CMR in low operative risk patients with a negative LDD test to obtain a higher sensitivity and NPV. Since DE CMR is easier to perform and carries a lower complication risk and since its sensitivity/NPV is higher than LDD CMR's specificity/PPV, DE CMR should probably be used as the first-line assessment. This approach has previously suggested by Kaandorp et al. (70); in their study, DE CMR and LDD CMR were compared head to head on the same patients in order to evaluate myocardial viability. The authors concluded that LDD CMR might be an option when patients have an intermediate extent of scar to ultimately differentiate viable from nonviable myocardium (70).

It is worth pointing out that the low specificity and PPV of DE CMR might be due to the fact that investigators have had to use a particular cutoff of 50% for research purposes in order to differentiate viable from nonviable myocardium. As described first by Kim et al. (10) and Van Hoe et al. (36) a few years later, myocardial viability should not be interpreted as an all-or-none phenomenon for 2 reasons: 1) although segments without any degree of hyperenhancement have a high PPV (92%), segments with partial hyperenhancement (0% to 50%) have a less predictable response to revascularization; and 2) different degrees of wall motion abnormalities have a major impact on myocardial recovery, with segments showing akinesia and dyskinesia demonstrating the best recovery (sensitivity 92%, NPV 96%, specificity 86%, and PPV 73%) (10,36).

In order to take the aforementioned situation into account, we carried out a subanalysis on DE CMR studies that reported their findings by quartiles. Our results mainly showed that using a cutoff of <0% to define viable myocardium significantly improves the specificity and PPV of this technique as compared with using a cutoff of 50%. On this basis, patients without any degree of hyperenhancement might not require LDD CMR to optimally differentiate viable myocardium. Yet, it is important to remember that the values obtained using a cutoff of <0% for DE CMR are not as high as those provided by LDD CMR (87%, 77% vs. 91%, 93%).

In addition to providing 1 of the best diagnostic accuracy values, CMR can also provide valuable information in assessing LV function, LV volumes, and the presence of either functional mitral regurgitation or aneurysm that might be suitable for repair at the time of CABG (71,72). Improvement

of LV systolic dysfunction is clinically important because LV ejection fraction is a major determinant of survival in patients with CAD (73). Although, no CMR study among the trials in our meta-analysis evaluated global LV function in terms of diagnostic accuracy, the ejection fraction increased from 41% to 47% ($p = 0.007$) in DE CMR studies, from 42% to 48% ($p = 0.03$) in LDD CMR, and from 37% to 41% ($p = 0.34$) in EDWT CMR.

Two shortcomings of CMR are worth mentioning. First, CMR is contraindicated in many patients with metallic implants. However, devices such as intravascular stents, most prosthetic cardiac valves, and prosthetic joints placed within the last 2 decades are considered "MRI safe." Pacemakers and implantable cardioverter-defibrillators are still considered a strong relative contraindication to CMR examination due to the risk of arrhythmia induction, device movement, and especially "lead heating" (74). However, a recent randomized clinical trial evaluated CMR safety of a new implantable cardiac device (MRI SureScan pacemaker system, Medtronic, Minneapolis, Minnesota) in 200 patients, with no CMR-related complications reported during or after the test (75,76).

Second, nephrogenic systemic fibrosis is a devastating (albeit extremely rare) potential complication in patients exposed to gadolinium-based contrast agents. This complication occurs almost exclusively in patients with moderate to severe renal disease, particularly those on dialysis (77,78). The Food and Drug Administration currently defines patients with an estimated glomerular filtration rate of <30 ml/min as "at risk" for this complication.

Clinical implications. In light of having no single test to accurately assess myocardial viability, it may be advisable to combine the assessment of the degree of transmurality scar tissue with DE CMR and the assessment of the contractile reserve with LDD CMR to obtain the best possible diagnostic and prognostic information. Here, it has been clearly demonstrated that DE CMR provides the highest sensitivity and NPV for predicting LV recovery of functionality after revascularization, whereas LDD CMR provides the highest specificity and PPV of any currently available test to evaluate myocardial viability. Supported by these results, patients with <50% of DE should undergo LDD CMR to precisely differentiate viable from nonviable myocardium. The latter technique might not be entirely necessary if patients have no hyperenhancement in the LV wall.

The recent multicenter trial of "Coronary-Artery Bypass Surgery in Patients with Left Ventricular Dysfunction" published by the STICH (Surgical Treatment for Ischemic Heart Failure) Investigators was carried out in order to evaluate whether there is any benefit in terms of morbidity and mortality between medical therapy as compared with revascularization therapy (79). This trial showed a significant, although modest, reduction in the risk of death, myocardial infarction, and other major cardiovascular events in patients randomized to CABG (79). Moreover, a subanalysis of the STICH trial assessing the value of myocardial viability assessment suggested that neither echocardiographic nor nuclear scintigraphic methods helped in selecting patients for revascularization (80). Hence, this study highlights the need to investigate the role of more reliable tests to evaluate patients with chronic LV dysfunction in whom a revascularization intervention is being planned. It has been clearly demonstrated in prospective trials that DE CMR has very low intraobserver and interobserver variability (81). Moreover CMR can also allow for a more comprehensive evaluation of virtually every aspect of the cardiac anatomy and function. Whether this will translate into increased ability to identify chronic ischemic patients who will benefit from revascularization remains to be determined.

Study limitations. An appropriate assessment of the diagnostic accuracy for EDWT CMR was not reached due to the limited number of studies and the high level of heterogeneity in specificity. There were few studies using CMR for the prediction of recovery of global LV function after revascularization. Similarly, no test evaluated improvement in heart failure symptoms or exercise capacity. Given the fact that a viability test is currently often chosen based on physician preferences, availability, or experience with the test, it might not be suitable to extrapolate these results widely. Other methods to evaluate myocardial viability using CMR have also been recently proposed. However, due to the small number of studies, they could not be included in this meta-analysis.

DE CMR and LDD CMR diagnostic accuracies could not be statistically combined in order to evaluate how adding these 2 methods will improve sensitivity/specificity upon each technique separately, given the fact that only 2 studies implemented both LDD and DE techniques on the same patients, and patient-level data was not provided in these articles. Finally, results from LDD CMR should be cautiously interpreted, given the borderline significance for publication bias demonstrated by Deeks's test.

CONCLUSIONS

Among CMR viability methods, DE CMR provides the highest sensitivity and NPV. Likewise, LDD CMR provides the highest specificity and PPV of any other modality. In light of these findings, integrating these 2 methods should provide increased accuracy in evaluating patients with chronic LV dysfunction being considered for revascularization.

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